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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/886,227	06/21/2001	Michael Samoszuk	034827-0201	5866

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER

1637

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12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/886,227	SAMOSZUK ET AL.
Examiner	Art Unit	
Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on November 18, 2002.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-21 is/are pending in the application.
4a) Of the above claim(s) 19-21 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-7 and 9-18 is/are rejected.

7) Claim(s) 8 is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892) 4) Interview Summary (PTO-413) Paper No(s). _____
2) Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) Notice of Informal Patent Application (PTO-152)
3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 12. 6) Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-18 in Paper No. 11 is acknowledged.

Claim Rejections - 35 USC § 112

2. Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 16, the word "sad analyses" is used in the last line. While it is assumed that this is a simple typo, it is unclear and therefore should be corrected. If "said" is intended, then correction is required. If "sad" is intended, it is unclear what limitation this word imposes.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-5, 7 and 9-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Menke et al (Electrophoresis (1995) 16:733-738) in view of Chen et al (Clinical Chemistry (1999) 45(8):1162-1167).

Menke teaches a method for determining the clonality of a T-cell receptor (TCR) rearrangement in a sample (see abstract) comprising:

(a) extracting nucleic acid from a human, formalin fixed, paraffin embedded tissue specimen or from blood monocytes (white blood cells) (see page 734, column 1, subheading "DNA extraction"),

(b) amplifying said nucleic acid by polymerase chain reaction with two TCR specific primers which amplify the VJ region to provide TCR DNA fragments (See page 734, subheading "PCR" and figure 1),

(c) analyzing said TCR DNA fragments using an electrophoretic gel with urea by temperature gradient gel electrophoresis (TGGE), wherein the presence of one or more discrete bands in said electrophoresis gel indicates the presence of a clonal TCR rearrangement (see page 734, column 2, subheading "gel electrophoresis" to page 735, column 1 and figure 2).

Menke suggests the use of skin biopsy specimens (see page 737, column 2).

Menke teaches the use of DNA migration markers (see page 735, figure 2, pBR 322 HaeIII digest) including positive controls for clonal T-cell rearrangements (see page 735, figure 3).

Menke teaches the use of the method for diagnoses of patients suspected of having lymphoma (see page 737, column 2).

Menke does not teach the use of TTGE in the place of TGGE.

Chen teaches the use of TTGE methods for the analysis of clonality in patients (see page 1163, column 2). Chen expressly motivates the use of TTGE as superior to TGGE (see page 1163, column 2). Chen teaches raising the temperature of the gel in a template dependent manner from temperatures as low as 53 C to as high as 64 C in a polyacrylamide gel with urea by incrementing the temperature 1.2 degree C/hour over 6 hours at 145 V. With respect to the voltage and temperature range, these are results optimizable variables which the ordinary practitioner recognizes depend upon the specific gel apparatus, concentration of gel. Thus, an ordinary practitioner would have recognized that the results optimizable variables could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific voltages or times was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the TGGE clonal analysis method of Menke by use TTGE in the place of TGGE since Menke recognizes a problem in detection is that "more sensitive electrophoresis techniques are required (page 737, column 1)". Chen provides the solution to this problem, and states "TTGE differs from TGGE, which has been reported several times, in that TGGE has a fixed temperature gradient from top to bottom of the gel. In TTGE, the temperature at any location of the entire gel is the same at any given time but changes with respect to time (temporal temperature). Thus, it is easier to modulate the temperature over time and provide a wider separation range that increases sensitivity (page 1163, column 2)". Chen further notes that "Thus, TTGE is simple and more cost effective without sacrificing sensitivity (see page 1167, column 1)". An ordinary practitioner, faced with the suggestion of Menke who desired more sensitive electrophoresis techniques and also faced with the desire for cost effectiveness in diagnostic assays, would have been motivated to solve this problem by using the TTGE method of Chen, since Chen expressly teaches that the method is more sensitive than TGGE, and also more cost effective, thereby resolving both concerns of the ordinary practitioner.

6. Claims 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Menke et al (Electrophoresis (1995) 16:733-738) in view of Chen et al (Clinical Chemistry (1999) 45(8):1162-1167) as applied to claims 1-5, 7 and 9-15 and further in view of Chott et al (J. Invest. Dermatol. (1996) 106(4):696-700).

Menke in view of Chen teach the limitations of claims 1-5, 7 and 9-15 as discussed above.

Menke in view of Chen do not teach comparing two lesions in a patient to determine if the identical clonal T cell rearrangements are present in each sample.

Chott teaches analysis of multiple lesions in the same patients in order to determine if the clonal rearrangements are the same (see abstract and page 698, columns 1 and 2). Chott expressly shows the situation where a patient has recurrences in the same location (see patient 7, page 699, figure 4, with four occurrences on the right forearm) as well as where different loci are present (see patient 11, page 698, table I, with occurrences on leg and back and buttock).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to apply the TTGE method of detection of clonality of T cells of Menke in view of Chen to the multiple lesions studied by Chott since it permits a determination of whether the disease is a clonal disorder as Chott notes "The results offer strong evidence that LyP is a clonal lymphoproliferative disorder and indicate that regressing lesions of LyP are clonally related to the malignant lymphoma of most LyP patients (page 696, column 2)". An ordinary practitioner would have been motivated to determine the clonality of the T cells since this would permit achievement of the goal of Menke, which is "monitoring minimal residual disease under therapeutic conditions (page 737, column 2)" in order to permit "an individualized therapeutic approach in lymphomas (page 737, column 2)". Thus, an ordinary practitioner would have been motivated to apply the method of Menke in view of Chen to the multiple lesion situation

of Chott in order to monitor the disease and determine whether the lesion is a regression or is a new lesion in order to individualize the therapeutic approach and increase the success of treatments.

7. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Menke et al (Electrophoresis (1995) 16:733-738) in view of Chen et al (Clinical Chemistry (1999) 45(8):1162-1167) as applied to claims 1-5, 7 and 9-15 and further in view of Theodorou et al (Blood (1995) 86(1):305-310).

Menke in view of Chen teach the limitations of claims 1-5, 7 and 9-15 as discussed above.

Menke in view of Chen do not teach analysis of lymph node samples.

Theodorou teaches the analysis of lymph node samples for clonality of T Cell receptor genes by PCR and DGGE (see page 305, abstract and column 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to apply the TTGE method of detection of clonality of T cells of Menke in view of Chen to the lymph node tissue of Theodorou since Theodorou states "The lymph node analysis by PCR showed a predominant T-cell clone in three of four biopsies (see page 309, column 1)". So an ordinary practitioner would have been motivated to analyse lymph node tissue since it would provide effective determination regarding the clonality of the T-cell population and since the analysis permits detection "even when the lymph node sample looks histologically benign (page 309, column 1)".

Allowable Subject Matter

8. Claim 8 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.
9. The following is a statement of reasons for the indication of allowable subject matter: Claim 8 is drawn to SEQ ID Nos: 3 and 4 which were not found in the prior art sequence search.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.


Jeffrey Fredman
Primary Examiner
Art Unit 1637

December 16, 2002